Original Article

Single-fiber Electromyography in the Extensor Digitorum Communis for the Predictive Prognosis of Ocular Myasthenia Gravis: A Retrospective Study of 102 Cases

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Abstract

Background: Single-fiber electromyography (SFEMG) abnormality in the extensor digitorum communis (EDC) was reported in ocular myasthenia gravis (OMG), which indicated subclinical involvement beyond extraocular muscles in OMG patients. The relationship between the abnormal findings of SFEMG in EDC and the probability for OMG to develop generalized myasthenia gravis (GMG) is unknown. This retrospective study aimed to determine the predictive value of abnormality of SFEMG in EDC of OMG patients.

Methods: One-hundred and two OMG patients underwent standard clinical diagnosis process and SFEMG test in EDC muscle when diagnosed and were clinically followed up for 5 years. The SFEMG data were compared between different clinical groups according to thymus status, onset age, and different outcome of OMG developing. Chances of progressing to GMG were compared between two different groups according to SFEMG and repetitive nerve stimulation (RNS) results, acetylcholine receptor antibody (AchRAb) titer, thymus status, and onset age.

Results: Abnormal SFEMG results were observed in 84 (82.4%) patients. The mean jitter, percentage of jitter >55 μs (%), and blocking were higher in OMG patients than in healthy volunteers. There were no statistical differences in jitter analysis between thymoma group and non-thymoma group ($P = 0.65$), or between the later OMG group and the later GMG group ($P = 0.31$), including mean jitter, percentage of jitter >55 μs (%), and blocking. Elderly group (≥45 years old) had a higher mean jitter than younger group ($t = 2.235$, $P = 0.028$). Total 55 OMG developed GMG, including 47 in abnormal SFEMG group while 8 in normal SFEMG group. There was no statistical difference in the conversion rates between the two groups ($\chi^2 = 0.790$, $P = 0.140$). RNS abnormality, AchRab titer, or onset age had no correlation with OMG prognosis ($P = 0.150$, 0.070, 0.120, respectively) while thymoma did ($\chi^2 = 0.510$, $P = 0.020$).

Conclusion: SFEMG test in the EDC showed high abnormality in OMG, suggesting subclinical involvement other than extraocular muscles. Nevertheless, the abnormal jitter analysis did not predict the prognosis of OMG according to clinical follow-up.

Key words: Extensor Digitorum Communis; Generalized Myasthenia Gravis; Ocular Myasthenia Gravis; Prognosis; Single-fiber Electromyography

Introduction

Myasthenia gravis (MG) is characterized by muscular fatigue due to a defect in neuromuscular transmission.[1] In ocular myasthenia gravis (OMG), weakness is limited to the extrinsic ocular muscles, and no facial muscles or extremity muscles are involved. Since gold standard tests are not available, the diagnosis of OMG is very difficult to make, in the case, neither clear clinical picture nor acetylcholinesterase inhibitor test was available. In 1970's, Ekstedt and Stalberg[2,3] introduced single-fiber electromyography (SFEMG) as an important method to evaluate neuromuscular transmission defects. Since then, its diagnostic value in MG has been evaluated in many studies,[4-6] in both extraocular muscles and extremity muscles. A remarkable sensitivity has been demonstrated in detecting subclinical neuromuscular transmission defects in

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MG and OMG. Abnormal SFEMG in extensor digitorum communis (EDC) muscle of OMG could demonstrate the subclinical involvement though there was no clinical weakness.[7,8] As subclinical abnormality could be found, would an abnormal jitter predict the prognosis of OMG? Rostedt *et al*.[9] have followed up 50 patients for 2 years and concluded that the SFEMG abnormality in EDC was not useful in predicting generalization in OMG patients in 2000. Here, we report our findings in a larger population of 102 OMG patients who were investigated and followed up for 5 years. We retrospectively reviewed the sensitivity of SFEMG in diagnosis, as well as its predictive value for prognosis in these patients.

Methods

Subjects

One-hundred and two OMG patients were enrolled in this study between 2003 and 2010. MG patients were recruited from Department of Neurology, Peking Union Medical College Hospital. All OMG patients had a confirmed diagnosis according to diagnostic criteria. The diagnostic criteria were as follows:[10] Extraocular muscle weakness in one or both eyes, ptosis or double vision, and remission after rest and severe fatigue at the initiation of the symptoms; fatigue of the affected muscle with fatigue test; a positive neostigmine test; or abnormal repetitive nerve stimulation (RNS) electromyography with a minimum decrement of 15% in extremities muscles and 10% in facial muscles; or abnormal serum acetylcholine receptor antibody (AchRab) level. Only patients who had SFEMG studies in the EDC muscle during the initial examination and pure ocular muscle weakness were included in the study. Patients with generalized fatigue symptoms and signs were excluded. The thyroid function test, thyroid autoantibody test, and chest computed tomography (CT) were also conducted, because MG is known to be closely associated with hyperthyroidism and thymus lesion.

The 80 age-matched healthy volunteers were all healthy relatives of the patients, with no neurological medical history and normal neurological examinations.

All patients were followed up with further treatment, including anticholinesterase, glucocorticoid, and immunosuppressants for at least 5 years. The protocol for this research study was reviewed and approved by the Institutional Review Board of Peking Union Medical College Hospital, and all participants gave informed consent.

Single-fiber electromyography

Cholinesterase inhibitors were withheld for 18–24 h before testing. SFEMG electrode (diameter for recording 2.5 μm) and a Counterpoint EMG instrument (Keypoint. 4ch, Medtronic, Denmark) were used for minimum voluntary contraction SFEMG test. Jitter was calculated as mean consecutive difference (MCD). The criteria for acceptable potential pairs were: Amplitude >200 μV; and rise time <300 μs. At least 10–20 pairs were recorded from the muscle. Abnormal SFEMG criteria included: Mean jitter >50 μs and/or more than 10% of pairs had jitter >55 μs, with or without blocking; blocking was the discharges dropped during a consecutive discharging when MCD ≥80 μs. Normal EDC SFEMG reference values were derived from our previous studies.[11,12]

Repetitive nerve stimulation

The facial nerve, axillary nerve or accessory nerve, and ulnar nerve were stimulated for 10 trains with stimuli of duration of 0.1 ms at low frequencies of 3 c/s and 5 c/s. RNS was considered as abnormal when the 4th compound muscle action potential (CMAP) had a ≥15% decrease compared with the first CMAP. High-frequency stimuli (50 c/s) were performed at ulnar nerve, and abnormal decrease was considered when the 75th CMAP decreased more than 30% compared to the first CMAP. If there was 100% increase of the 75th CMAP compared with the first CMAP, the case would be excluded because of possible diagnosis of Lambert-Eaton syndrome.

Acetylcholine receptor antibody

AchRab titer was measured by enzyme-linked immune-sorbent assay according to Lindstrom's method[13] before January 2013, P/N (patient's optical density [OD]/normal control's OD) ≥1.2 was abnormal. Radioactive isotope-based radioimmunoassay[14] was introduced from February 2013, and titers ≥0.4 nmol/L was regarded as abnormal.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22.0 (SPSS Inc., USA). Measurement variables were presented as mean ± standard deviation (SD). The upper limit of normal was set at the 95th percentile for non-Gaussian distributions. Values were compared between groups by Mann-Whitney *U*-test. Enumeration variables were analyzed by Fisher test or Chi-square test. A $P < 0.05$ was considered as statistically significant.

Results

Subjects

One-hundred and two OMG patients were recruited. The mean age of onset was 40.7 ± 15.6 years, ranging from 16 to 81 years; there were 49 males and 53 females. The first symptoms included ptosis in monocular or binoculus and diplopia. The mean duration from initial symptom to definite diagnosis was 1.5 ± 1.3 years, ranging from 1 month to 10 years. The AchRab titer was tested in all patients and was elevated in 48 (47.1%) patients. RNS was performed in all the OMG patients when diagnosed, and 35 (34.3%) had decreased in different nerves. Chest CT revealed 19 abnormal thymus lesions, including thymoma in 15 and thymus hyperplasia in 4 after thymectomy and pathology revealed.

There were 37 males and 43 females in the healthy control group. The mean age was 42.3 ± 18.6 years, ranging from 21 to 75 years old.

Single-fiber electromyography

SFEMG studies revealed abnormality in 84 of 102 OMG patients (82.4%). The mean MCD was 54.5 ± 21.9 μs, which was much higher than healthy controls (27.6 ± 8.2 μs) ($t = 3.428$, $P = 0.001$). All SFEMG

parameters showed the difference between OMG patients group and healthy controls. The mean jitter, percentage of jitter >55 μs (%), and number of blocking were all higher in the OMG patient group [Table 1].

There was no correlation observed between jitter value and thymus lesion. The mean jitter, percentage of jitter >55 μs (%), and blocking rates were not higher in the thymoma group [$t = 0.761$, $P = 0.470$, Table 2].

Elderly patients (onset age ≥45 years, 46 patients) had higher mean jitter and other parameters than younger patients (onset age <45 years, 56 patients) [$t = 2.235$, $P = 0.028$, Table 2].

Clinical prognosis

We compared the frequency of generalization between patients with different SFEMG results. Total 55 OMG developed generalized myasthenia gravis (GMG) in the follow-up, 47 of 84 patients in the abnormal SFEMG group while 8 of 18 in the normal SFEMG group. There was no significant difference between the two groups [$\chi^2 = 0.790$, $P = 0.140$, Table 3]. In addition, SFEMG parameters, including mean jitter, percentage of jitter >55 μs (%), and blocking, showed no difference between those who developed GMG ($n = 55$) and those who remained ocular ($n = 47$) [$t = 1.424$, $P = 0.190$, Table 2].

There were no correlations between OMG prognosis and SFEMG abnormality, RNS abnormality, AchRab abnormality, or onset age [$P = 0.140$, 0.150, 0.070, and 0.120, respectively, Table 3]. However, the patients accompanied with thymoma had a high risk of developing GMG [$\chi^2 = 4.810$, $P = 0.020$, Table 3].

In the later GMG group ($n = 55$), 38 patients developed nonocular myasthenic symptoms within 2 years after the initial symptoms onset, and 17 patients developed GMG 2 years after. These two groups showed no differences in SFEMG parameters, including mean jitter, percentage of jitter >55 μs (%), and blocking.

Table 1: Jitter analysis in patients and healthy controls

Items	Patients ($n = 102$)	Healthy controls ($n = 80$)
Number of jitter	1697	1180
Mean jitter (μs), mean ± SD	54.5 ± 21.9	27.6 ± 8.2
Percentage jitter >55 μs (%), mean ± SD	21.7 ± 20.6	0
Blocking (%), mean ± SD	9.0 ± 8.3	0

SD: Standard deviation.

Discussion

SFEMG is the most sensitive test for detecting neuromuscular transmission disorder as reported by us previously[11] and by other researchers.[7,8] Since a gold diagnostic standard is not available in MG, abnormal SFEMG in accordance with clinical fatigue could contribute to the diagnosis. The sensitivity of RNS and AchRab titer in patients with pure OMG are considerably low, as were 34.3% and 47.1%, respectively in our study. SFEMG plays an important role in the diagnosis of the abnormality of the neuromuscular junction.

Abnormal SFEMG findings were found in the EDC muscle in approximately 82% of our OMG patients. This indicated that these patients have a decreased safety margin of neuromuscular transmission even in muscles other than extraocular muscles, which showed no clinical weakness. The percentage of abnormality was a little higher than our previous report[11] and other studies.[9] Since the SFEMG technique is very sensitive to neuromuscular transmission defect, the abnormal jitter could be found in any condition of nerve regeneration. The high rate of abnormal SFEMG findings in our study is perhaps due to a high percent of old participants in the group, who had underlying nerve regeneration of EDC though they denied cervical root degeneration. In our study, the mean jitter, percentage of jitter >55 μs (%), and blocking were raised in elder age, which may support our speculation. Onset age had no correlation with OMG prognosis. And, this conclusion conformed to the same results from Dr. Yu's analysis published in 2010.[15]

The abnormal jitter of EDC implied more subclinical involvement in autoimmune, but no correlation was found between the abnormality of SFEMG and existence of thymoma. Our result was the same as that reported by Emeryk-Szajewska *et al*.[16] The impact of thymoma on the risk of developing GMG was verified in our study.

The remarkable correlation between SFEMG and RNS, SFEMG and AchRab was observed in our previous report,[11] and we did not repeat in this study. In the larger population study with 5 years follow-up, we found that the prognosis of OMG has no relationship with SFEMG, RNS, or AchRab.

Table 2: Jitter analysis according to different clinical groups, mean ± SD

Items	Thymus		*t*	*P*	Onset age		*t*	*P*	Prognosis		*t*	*P*
	Thymoma ($n = 15$)	Non-thymoma ($n = 87$)			<45 years ($n = 46$)	≥45 years ($n = 56$)			Later OMG ($n = 47$)	Later GMG ($n = 55$)		
Mean jitter (μs)	52.9 ± 18.4	56.3 ± 25.7	0.761	0.47	50.9 ± 20.8	58.5 ± 27.1	2.235	0.028	51.5 ± 22.3	56.1 ± 23.6	1.424	0.19
Percentage Jitter >55 μs (%)	20.9 ± 17.8	22.6 ± 21.5	0.612	0.58	19.3 ± 14.4	24.4 ± 20.3	2.064	0.031	19.9 ± 16.5	22.4 ± 21.2	0.936	0.36
Blocking (%)	9.7 ± 9.5	8.1 ± 7.3	1.330	0.13	8.2 ± 7.9	10.7 ± 9.1	2.101	0.030	8.1 ± 7.7	10.0 ± 9.2	0.979	0.31

SD: Standard deviation; OMG: Ocular myasthenia gravis; GMG: Generalized myasthenia gravis.

Table 3: OMG prognosis in different clinical groups (*n*)

Items	Later OMG (*n* = 47)	Later GMG (*n* = 55)	Total number	χ^2	*P*
SFEMG					
Abnormal	37	47	84	0.790	0.140
Normal	10	8	18		
RNS					
Abnormal	17	18	35	0.130	0.150
Normal	30	37	67		
AchRab					
Abnormal	19	29	48	1.540	0.070
Normal	28	26	54		
Thymus					
Thymoma	3	12	15	4.810	0.020
Non-thymoma	44	43	87		
Onset age					
<45 years	24	32	56	0.510	0.120
≥45 years	23	23	46		

OMG: Ocular myasthenia gravis; SFEMG: Single-fiber electromyography; RNS: Repetitive nerve stimulation; AchRab: Acetylcholine receptor antibody; GMG: Generalized myasthenia gravis.

Since there is no reliable parameter at present to predict the tendency for OMG patients to develop GMG, we suspected that the SFEMG abnormality in EDC muscle might imply an OMG patient to be "subclinical GMG" from a clinical neurophysiology point of view. But in this study, there was no difference of prognosis of OMG between normal and abnormal EDC SFEMG groups. There were no differences in jitter analysis between the two groups of different clinical outcomes (later OMG and later GMG). Our results suggested that SFEMG in the EDC muscle could not predict the development of generalized myasthenic weakness in pure OMG patients. Although SFEMG measurement of jitter in the EDC muscle can demonstrate abnormal neuromuscular transmission in many OMG patients, it appears to be not useful in predicting generalization in these patients. The abnormal SFEMG findings indicating subclinical involvement could not predict the development of the disease. This study also does not support the fact that the prognosis of OMG can be definitely altered by active treatment of the disease. The link between abnormal findings in the SFEMG in the EDC muscle and prognosis of OMG appears to be very tenuous.

SFEMG of other muscles in OMG also showed high abnormality rates. SFEMG of superior rectus and levator palpebralis muscle complex were found abnormal in 100% of OMG, and orbicularis oculi in 62% of the patients.[6] But their relationship with the prognosis was unknown. Abnormal SFEMG findings in some extremity muscles including extensor digitorum (hallucis) comminus (EDC, 75.5%) had no relationship with the risk of the generalization of OMG,[15] so the abnormal SFEMG results and the prognosis of OMG might had no relation.

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Conflicts of interest

There are no conflicts of interest.

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